Technical Note

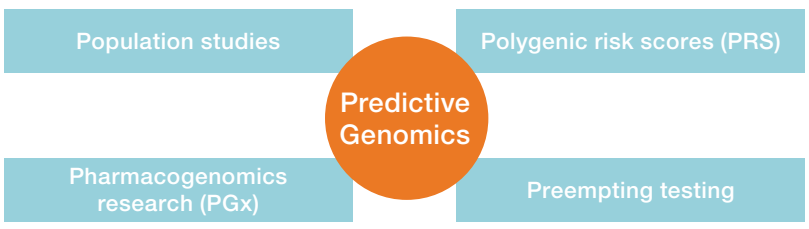
Imputation-aware microarrays offer more power than low-pass sequencing

Contributors: Anu Mittal, Karl J. Schweighofer, Jeremy N. Gollub, Jeanette Schmidt

Recent studies suggest that whole genome low-pass sequencing (LPS) equals or exceeds the accuracy obtained with arrays. Here we assess the relative performance of LPS with respect to population optimized1 and rare variant optimized2 genotyping arrays. We show that advanced genotyping algorithms allow much higher accurate direct genotyping of rare variants and variants in difficult regions than 1x LPS. Genome wide imputation coverage is similar for arrays and 1x LPS. The only LPS that is price competitive with arrays is 0.1x LPS, which lags significantly behind array performance in both.

Introduction

- High genome-wide imputation accuracy and reliable detection of rare and challenging variants are the cornerstones of predictive genomics.
- We implemented algorithmic improvements and design capabilities to provide a boost in imputation performance and rare variant calling accuracy for arrays.



Results

Genome-wide imputation performance

- High imputation accuracy in diverse ethnicities is key for the success of polygenic risk scores (PRS).
- For common variants, arrays show much higher accuracy than the cost competitive 0.1x LPS.
- Arrays show imputation accuracy similar to much costlier 0.5x - 1x LPS.
- Low frequency variants cannot be reliably imputed with either arrays or LPS, but can be directly assayed with arrays.

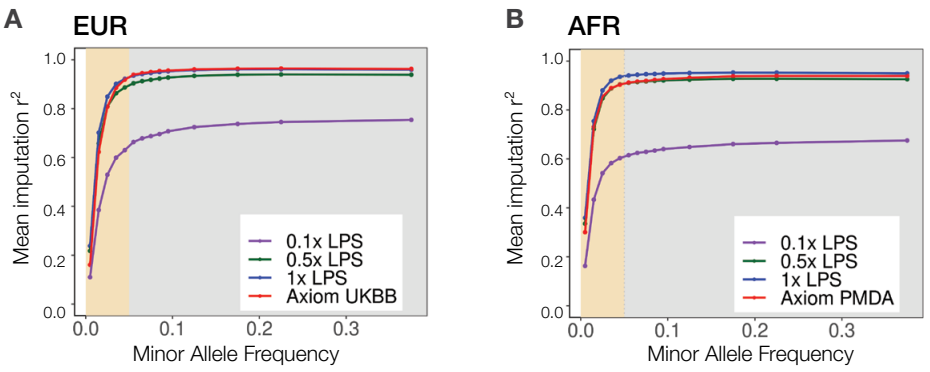


Figure 1. Imputation accuracy for different technologies in EUR (Figure 1a) and AFR (Figure 1b) cohorts.

Genotyping of rare variants

- Rare variants can be directly genotyped on arrays with high accuracy.

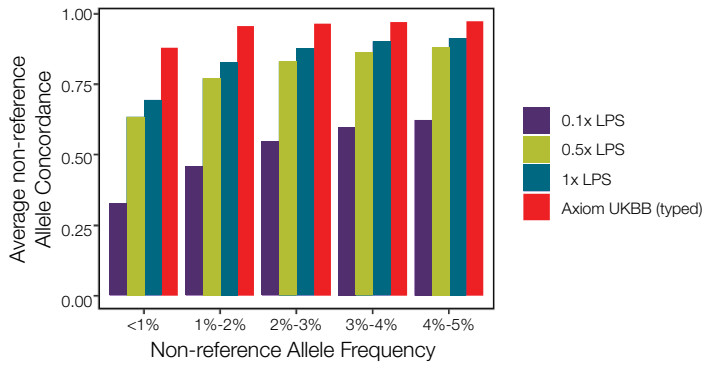


Figure 2. Non-reference allele concordance of low-frequency variants.

Performance of carrier screening variants

The table below shows the genotyping concordance of 38 pathogenic carrier screening variants involved in severe disease traits (such as CF) over a set of 32 samples that are carriers for at least one variant.

- Compared to LPS, microarrays show higher accuracy of mutation detection over a range of mutation types.

Table 1. Genotyping concordance of pathogenic carrier screening variants.

	Overall	MAF<1%	MAF 1–5%	MAF>5%
0.5x LPS	88.95%	72.4%	88.2%	92.8%
1x LPS	97%	96.6%	94.1%	97.6%
Arrays	100%	100%	100%	100%

Performance of Pharmacogenomics (PGx) variants

- Many PGx variants occur in difficult to genotype genomic regions.
- Arrays show higher genotype concordance of the PGx variants compared to LPS.

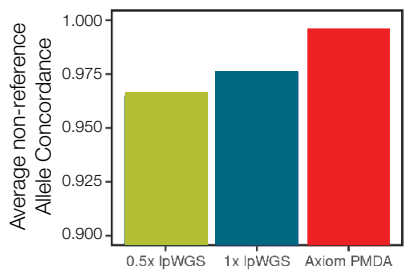


Figure 3. Non-reference allele concordance of pharmacogenomic variants.

- As an example, CYP2D6_100C>T variant is associated with reduced drug clearance and tonic-clonic seizures.
- Two samples homozygous for the pathogenic allele were correctly genotyped on Axiom PMDA.
- Both samples showed low coverage in the target regions and were incorrectly imputed with 0.5x and 1x LPS

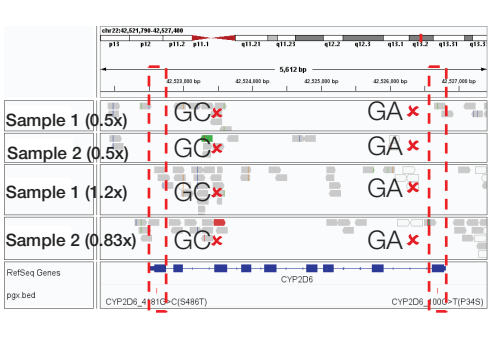


Figure 4. Pileup of LPS reads for two samples sequenced at 0.5x and 1x.

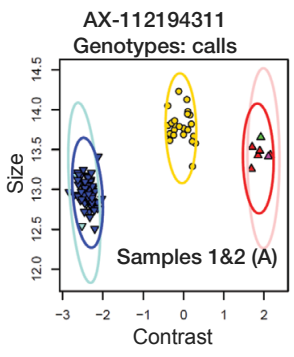


Figure 5. Clearly separated genotype clusters using Axiom microarrays.

Conclusion

Axiom microarrays offer advantages over low pass sequencing (LPS) in various ways:

- Imputation-aware designs offer high coverage and accuracy for diverse ethnic populations.
- Arrays can accurately genotype rare variants, variants in challenging genes, insertion-deletions and copy number variation to support key research applications, e.g., PGx, carrier screening, blood typing, HLA typing and more.

References

1. Hoffmann et al., *Genomics*. 98(6):422-30. (2011)
2. http://downloads.thermofisher.com/Axiom_Analysis/tech-note-Axiom%20-RHA_final_Rev_0.6.pdf

Learn more at **thermofisher.com/predictive-genomics**